DNA Viruses

Introduction

The viruses in this lesson are all DNA viruses. The fact that you are learning them together in a single lesson will help carve out a spot in your memory, a mental clustering to help you remember which viruses are the DNA viruses. The lesson IS the advanced organizer. The map of the lesson at the end of the introduction is your visual representation of the lesson, and therefore also which DNA viruses are DNA viruses, separate from the other viruses that are not in this lesson.

DNA viruses have structural and replication similarities, as discussed in the next section. The virology categorization system sees them as similar. However, the diseases they cause are NOT similar. This lesson focuses primarily on the diseases these viruses cause and the mechanisms behind those diseases. The section headings are named by the virus. Because we have clustered these DNA viruses together, and all DNA viruses share similar microbiology, we can say once, up front, that every virus in this lesson is a DNA virus, is double stranded, is icosahedral, and may be enveloped. That means we are able to focus on the diseases' presentation, recognizing the clinical syndrome and associating it with the right virus.

We will not discuss poxvirus (smallpox), as it exists only at the CDC under lock and key; it has been eradicated from the planet. We will not discuss hepadnaviruses, either, in this lesson, reserving that discussion for the hepatitis lesson. The viral size increases from left to right. The lesson is organized by size of virus, starting with the smallest and working our way larger.

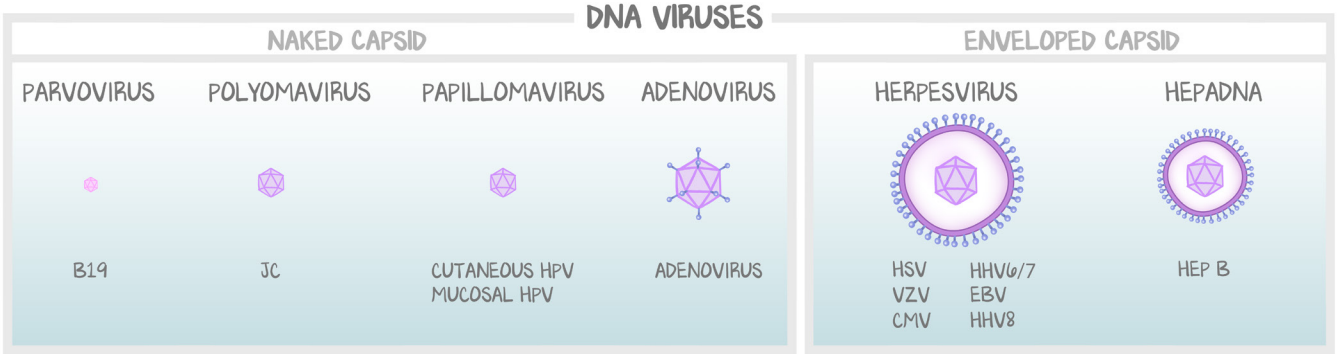

Figure 3.1: DNA Viruses
From left to right, the DNA viruses increase in size. The lesson progresses in the same order. The main focus is on the virus name, though we do categorize by virus family. Come back here to reference the size, shape, and order of virus.

DNA Virus Reminder

We learned from the first two lessons in this Virus series that we can make assumptions about the structure and function of these viruses because they are all DNA viruses, therefore limiting the amount of detail we'll need to memorize. Here it is again, summarized:

All DNA viruses are **double stranded** (except parvovirus).
All DNA viruses are **icosahedral**.
All DNA viruses replicate in the **nucleus**.
All DNA viruses use **host DNA-dependent RNA polymerase** after reaching the nucleus.
Herpesviruses and Hepadnaviruses Have an **envelope**; the rest do not, and are naked viruses.

From here on, we go virus by virus. We aren't going to say, "double stranded, icosahedral, nucleus, DdRp," in every virus. You can assume this section is applied to all the viruses that follow, unless exceptions are called out. As with parvovirus.

Parvovirus

Parvovirus is the smallest known virus. Its genome is so small, it codes for just two proteins. Inherently, then, parvovirus cannot manipulate the rate of transcription, and is entirely reliant on the host polymerases. This effectively means that parvovirus cannot replicate unless the cell it is in is undergoing replication. Parvovirus is **single stranded**, the exception to the rule that all DNA viruses are double stranded, and it lacks an envelope (is a **naked virus**). Parvovirus **B19** is the only serotype known to cause human disease. B19 causes **erythema infectiosum** (fifth disease or slapped-cheek syndrome), a mild febrile illness in children that results in bright red cheeks. It is one of the five classic childhood exanthems (the first four being varicella, rubella, roseola, and measles) and thus its name, "fifth disease." Following exposure, there is an incubation period of approximately one week, **high fevers** for a week, an asymptomatic honeymoon period for a week, then a week's worth of **the slapped-cheek rash** and **arthralgias**. These kids hurt, they feel miserable, but thankfully, the disease is self-limiting.

B19 infects **erythroid precursors**. Because it is a naked virus, it lyses its victims. In patients without a chronic hemolytic anemia, the bone marrow doesn't notice the lost red blood cell precursors. In patients who **do have chronic hemolytic anemia**, where the blood count is always a little low but sustained by ongoing erythrocyte production, the temporary interruption in that production results in **aplastic anemia**. This is often tested in regard to **sickle cell disease**, though any chronic hemolytic anemia would result in the same outcome. Transfuse patients through the aplastic crisis, and they will be fine. B19 is self-limiting; there is no treatment, no vaccine, and no sequelae.

Papillomavirus

Human Papilloma Virus (HPV) is a small, circular DNA virus. It is a **naked** virus. Over 100 types of HPV have been identified, classified into 16 groups. The good news is that you need to be familiar with about five types. There are two distinctions of importance for clinical practice—what type of epithelium they infect (tropism) and whether they cause cancer. There are **cutaneous HPV** serotypes that infect keratinized stratified epithelial (skin) cells and produce warts. These do not cause cancer. Plantar warts (warts on the foot) are caused by serotypes 1, 2, and 4. Anogenital warts, called **condyloma acuminatum**, are commonly caused by **6 and 11**. There are **mucosal HPV** serotypes that infect nonkeratinized stratified squamous epithelial cells (mouth, throat, vagina, anus, and penis) that do cause cancer. These are serotypes **16 and 18**. HPV causes a **persistent infection**. While it is a naked virus and must be cytolytic—exiting the cell requires lysis—it does so in tissue that sheds the outer layer anyway. HPV survives in epithelial precursors of the basal layer and lyses only the cells that are being shed.

Cutaneous HPV causes **warts**. HPV enters the basal layer of keratinocytes through breaks in the skin. Once inside the basal cells, early genes promote replication of the epithelial cells. More cells result in the thickening of the stratum basale and stratum spinosum. Expression of viral genes then correlates with the expression of specific keratins. As the keratinocyte differentiates, HPV switches from replication in the stratum spinosum to production and assembly of capsid proteins in the stratum granulosum, to final release of virus with release of the keratinocyte in the stratum corneum. Benign warts develop as a product of excess cells and abnormal keratinization. **Warts are contagious** but aren't cancerous, even with the increased proliferation. Surgically treating warts gets rid of them. This can be achieved by burning them off, freezing them off, or cutting them out. Stimulators of innate inflammatory responses such as **imiquimod** can accelerate healing. Topical or intralesional **cidofovir** can treat warts by selectively killing HPV-infected cells. It is a prodrug, activated only by viral genome, and subsequently induces apoptosis of the host cell.

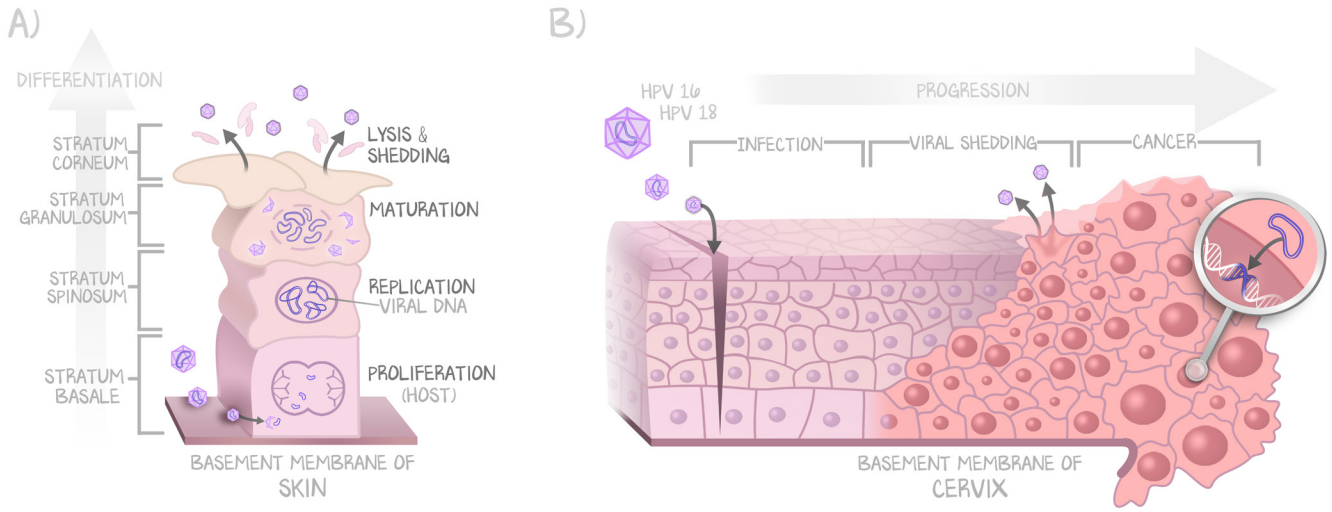

Figure 3.2: Human Papilloma Virus
(a) How HPV is an acute lytic infection for the cell, but a chronic infection for the patient. Normal keratinocyte maturation starts just as any cell—nucleus, ribosomes, mitochondria, etc. The farther toward the apical surface, the further differentiated the cell gets. Keratinocytes degrade their nucleus, mitochondria, and ribosomes, making room for more and more keratin. The most differentiated keratinocyte is one that is pure keratin, and forms the stratum corneum. These are not dead keratinocytes, only fully differentiated. The final act of the cell is to sever its desmosome, its connection to the rest of the cell layer, and be shed off into the wind. HPV infects the stem cells of the stratum basale and induces proliferation. Only when the keratinocyte differentiates does HPV begin replicating its genome in the stratum spinosum. As the nucleus is degraded in the stratum granulosum, late genes construct capsid and viral proteins. In the stratum corneum, just before the cell itself is shed, HPV assembles and lyses the keratinocyte. HPV infections of keratinized squamous epithelium (skin) do not cause cancer. (b) HPV types 16 and 18 cause cervical cancer. They infect the stem cells in the basal layer, induce proliferation, and induce mutations in DNA, leading to malignant transformation. HPV that infects the nonkeratinized squamous cell epithelium of the anus, oropharynx, and vagina does cause cancer.

Mucosal HPV infects the lining of the male urethra. Semen is passed through the infected urethra, which acts as a vessel to deliver HPV to a new host. Wherever semen goes, HPV can go. And whatever infected tissue a penis can reach can infect the penis. Not all subtypes that affect the mucosal epithelium are oncogenic, but the two you should know are. Subtypes **16 and 18** are termed high-risk strains because they contain **oncogenes**. HPV gene E6 codes for a protein that binds to p53 and accelerates its degradation, thereby decreasing apoptosis. HPV gene E7 codes for a protein that inhibits the retinoblastoma gene, Rb, thereby accelerating the cell cycle, promoting unrestricted growth. 95% of cervical cancers are associated with HPV infection. 70% of cervical cancers have HPV DNA incorporated into the host cell genome. Breaking the circular HPV DNA at E1 or E2 allows for integration with host DNA. That breaking prevents viral replication but leaves other viral genes, such as E6 and E7, transcriptionally active. Cervical cancer is now the most preventable cancer we have. Since almost all cases of cervical cancer are caused by a sexually transmitted infection with a virus of known subtypes, **vaccinating against HPV subtypes prevents cancer**. The latest vaccines cover the subtypes known to cause cancer (16 and 18) as well as those that typically cause condyloma acuminatum (6 and 11). **Vaccination is not a replacement for a Pap smear,** for cervical cancer screening. Regular Pap smears are still recommended for women not infected, women infected, and women vaccinated alike. The cancer we cannot prevent with vaccination we will catch as premalignancy with screening. No one should get cervical cancer. Every woman should receive regular Pap smears.

SYNDROME	COMMON
Plantar warts	1
Common warts	2, 4
Benign head- and neck-tumors	6, 11
Condyloma acuminatum	6, 11
Cervical cancer	16, 18

Gardasil 9 covers 6, 11, 16, 18, 31, 33, 45, 52, and 58	Tetravalent
Gardasil covers 6, 11, 16, 18	Nine-valent
Cervarix covers 16, 18	Divalent

Table 3.1: HPV Serotypes and Vaccines

270+ Polyomaviruses

Polyomaviruses are the same size as papillomavirus. They used to be in the same family. Now, they are separated. The thing to know is **JC virus** (JCV). JCV is ubiquitous, and is asymptomatic in almost all patients. In immunocompromised patients, JCV is activated, spreads to the brain, and causes **progressive multifocal leukoencephalopathy** (PML). PML lesions are demyelinated, with unusual large astrocytes and oligodendroglial cells with very large nuclei. It is a progressive demyelinating disease that affects all functions—motor, sensation, balance, coordination. There is nothing to do for it. The diagnosis is confirmed on brain biopsy on autopsy.

Adenovirus

There are 100 serotypes, and 52 of them cause disease. Burdening yourself with serotypes is too cumbersome and not clinically meaningful like it was for HPV. That is because adenovirus is a **naked** virus, and so is **cytolytic**. Unlike HPV, adenovirus causes only **acute illnesses** that **cannot be treated**. They are self-limiting and run their course. Adenovirus causes pharyngoconjunctivitis (pink eye), gastroenteritis (diarrhea), and atypical pneumonia, amongst others. It more commonly affects children and the immunocompromised. The virus is spread through aerosols or the fecal-oral route, infecting the mucosal epithelium of the oropharynx. Hands spread the virus to the eyes. Because it is naked, it is resistant to drying, detergents, and even gastrointestinal acid. Crowds and close proximity (schools, military barracks) promote the spread. **Military recruits** are provided an **oral vaccine**. Everyone else should wash their hands, chlorinate their pools, and keep febrile children home from school. There is a lot we know about adenovirus, and now there may be a way to use adenovirus to deliver genes for correction of human disease. While that sounds cool, you should see: "*adenovirus = pink eye in everyone and diarrhea/vaccine in military barracks.*"

Herpesvirus Family

When someone uses the words "herpes virus" in relation to disease, they are probably using it to mean the herpes simplex virus, the thing that causes the syndrome "herpes," the blistering disease of the mouth and/or genitals. Herpes simplex virus does cause the colloquial herpes syndrome, but is just one of the members in the herpesvirus family. All herpesviruses are DNA viruses—double-stranded DNA, icosahedral capsids, they replicate in the nucleus—and **are enveloped**. All herpesviruses share common features of their virion morphology, mode of replication, and capacity to establish latent and recurrent infections. That's the way virologists categorize viruses. That does not help YOU recognize or treat disease. They do not share similar presentations, disease courses, or treatment options. There are overlaps that will confuse you. There are some blanket statements we can make before we get started on the viruses themselves. But while the remainder of the infections in this lesson are caused by human herpes viruses (HHV) and share some pathologic findings, you should learn the diseases they cause as distinct entities.

SUBFAMILY	VIRUS	PRIMARY TARGET	LATENCY SITE	DISEASE
HHV-1	Herpes simplex 1	Squamous cells	Neuron	Cold sores, genital herpes (acute and latent)
HHV-2	Herpes simplex 2	Squamous cells	Neuron	Cold sores, genital herpes (acute and latent)
HHV-3	Varicella-zoster	Squamous cells	Neuron	Chicken pox (acute), shingles (latent)
HHV-4	Epstein-Barr	B cells	B cells	"Mono" (acute), lymphoma (transform)
HHV-5	Cytomegalovirus	Leukocytes	Myeloid stem cells	Asx exposure CMV retinitis AIDS, CMV rejection (transplant)
HHV-6	Roseola	N/A	N/A	Kids get a fever, then a rash as fever breaks
HHV-7				
HHV-8	Kaposi's sarcoma related virus	Endothelial ells	B cells	Purple cancers of vessels in AIDS

Table 3.2: Herpesvirus Family
This table acknowledges the nomenclature of HHV viruses, encourages the use of the virus name rather than the subfamily title, and shows overlapping similarities of viral types.

Herpesviruses are large viruses with many gene products, making their life cycle and control of the cell immensely complex. So we're not going to get into the weeds. They are enveloped. Because they are enveloped they are able to bring enzymes and proteins along with them when they infect the next cell. Within the envelope, between the membrane and the capsid is cytoplasm. When a herpesvirus virion is assembled, it is loaded with the DNA viral genome and capsid, the nucleocapsid, and transcription factors. Herpesviruses depend on **host DNA-dependent RNA polymerase** to get things started, producing mRNA from the viral genome. The viruses must also compete with host cell's gene transcription. By brining transcription factors with it, herpesvirus can trick the host DdRp into transcribing viral genes ahead of nuclear genes. The transcription factors promote expression of **immediate early genes**. The product of these immediate early genes are more transcription factors, but transcription factors for **early genes**. This produces a feedforward loop—the transcription factors brought with the virus initiate transcription of genes that are themselves transcription factors. Only the early genes code for the proteins the virus needs to replicate. Early genes code for **virus-encoded DNA-dependent DNA polymerase** and **thymidine kinase**. Thymidine kinase is a viral enzyme that provides more thymidine, increasing the availability of nucleic acids for genome replication. Thymidine kinase is how we have therapeutic options to treat herpesvirus. The virus is a DNA virus. To replicate it needs DdDp to make a copy. Waiting for host DdDp to replicate the virus would mean only one new copy would be made every cell division. Viral DdDp replicates the genome but lacks the regulation of host cell DdDp.

The accumulation of transcription factors and viral genome promotes expression of **late genes**. Late genes are expressed as the host cell's resources are dried up, the virus ready to move on to the next cell. Some of late gene expression is the generation of the capsid and glycoproteins for assembly. Some of the late gene expression is the production of enzymes that **consume the host cell**, digesting its DNA to obtain nucleotides for more genome, resulting in cell death. Assembly occurs through empty procapsids in the nucleus that are filled with DNA virus, then bud into and out of the endoplasmic reticulum, acquiring their envelope. You might think they were not cytolytic, possessing an envelope. However, herpesviruses are greedy, and their final act before departing the host cell, after having already accelerated its death by stealing every last nucleotide, is to lyse the cell. Cell death means that herpesviruses can cause only acute disease.

If the virus gets into cells that are incapable of transcribing those early genes, a **latent infection** is established. In particular, **neurons** (HSV-1, HSV-2, VZV) are not only unable to transcribe the early gene products, but can transcribe **latency-associated transcripts** (LATs), untranslated RNAs that encode micro-RNAs that inhibit the expression of early genes. They make RNA that keeps their own replication silenced. They persist. And that's why reactivation can occur—without replication of the virus in neurons, without activation of the gene products that would lead to cell lysis, the virus can lie dormant. Reactivation occurs in one neuron, resulting in the death of that one neuron, but the virus is able to travel down the neuron to reinfect the skin or mucosal surface. Acute disease with a limited course, but the reservoir of neurons is preserved. HSV and VZV use neurons; EBV and HHV8 use B cells; CMV uses myeloid precursors.

Herpesviruses cause **inclusion bodies** and **syncytia**. Other viruses can cause inclusion bodies and syncytia. Therefore, they are not pathognomonic, but are characteristic clues if given a slide to interpret. HSV, VZV, and CMV form intranuclear inclusions (the nucleus, normally spotty with euchromatin and heterochromatin, becomes one solid dark color) and perinuclear halos (ring of totally clear cytoplasm around the darkened nuclear inclusion). This type of inclusion body is called **Cowdry type A**. It is less important you can name it and more important you can recognize it. **Syncytia** are multinucleated giant cells formed by the fusion of individual cells, all infected by the virus.

Herpes Simplex Virus: HSV-1 and HSV-2

These viruses are **transmitted in saliva** and **vaginal secretions**. The "mixing and matching of mucous membranes" allows it to spread. We used to separate HSV-1 "for the face" (cold sores, fever blisters) and HSV-2 "for the genitals" (genital herpes), but modern sex practices have allowed for copious traffic between the two body parts, so now, "herpes is herpes." If you see a vesicle on an erythematous base on the mouth or genitals ("mucocutaneous"), it is herpes, a chronic condition, and can be treated with acyclovir. But because Step 1 does care about incidence and prevalence, we need to be specific. **Genital herpes** in the United States is about half HSV-1 and half HSV-2. Worldwide, in regard to all herpetic disease regardless of its location on the body, **HSV-1 is more common**. It is spread by oral contact (kissing) or through the sharing of drinking glasses, toothbrushes, or other saliva-contaminated items. More than 90% of people living in underdeveloped areas have the antibody to HSV-1 by 2 years of age.

Bottom line is this: don't make out with someone who has a fever blister on their lip—they have herpes and can give it to you. But chances are that their herpes wasn't contracted as a sexually transmitted infection. Also stop judging. You don't know how they got it. But still don't kiss it. Also don't make out with a penis with a fever blister—it has herpes and can give it to you. Chances are that their herpes was contracted sexually.

Herpetic lesions present with a **painful burning prodrome** before the vesicles erupt. The vesicles appear wherever the epithelium was infected. HSV doesn't usually disseminate, there isn't a viremia, so where the patient gets lesions will be where the patient GOT the lesions. The lesions are described as **multiple small vesicles**, each on its own **erythematous base**. If the vesicle is unroofed, it may appear as an ulcer. This is the acute infection. If it occurs on the genitals, it is called genital herpes. If it occurs on a finger, it is called herpetic whitlow. If it occurs on the lips, it is referred to as cold sores or fever blisters. If it occurs in the throat, it is called herpes pharyngitis. The virus can be identified in a **Tzanck smear**, a scraping of the base of one of these lesions, showing the inclusion bodies and syncytia. Tzanck smear is inferior to **HSV PCR** for diagnosis, but you should still be able to recognize the inclusions on a smear.

Two infections are worth calling out as special.

HSV encephalitis is a viral infection of the brain. HSV encephalitis is usually caused by HSV-1 because HSV-1 is so much more prevalent worldwide. It affects the **temporal lobe**. The destruction of cells in the CSF results in **many RBCs in the CSF**. The patient presents like a meningitis—fever, headache, and a stiff neck. Seizures are common. A lumbar puncture will reveal not thousands of neutrophils (as would be seen in bacterial meningitis) but hundreds of lymphocytes and lots of RBCs. The only viral encephalitis that can be treated is HSV encephalitis. HSV is the most common cause of sporadic viral encephalitis worldwide. The treatment is with **intravenous acyclovir**. It is treated presumptively while the CSF is assessed with the confirmation **HSV PCR**.

Neonatal HSV can easily be prevented. If it is not, a mother who gives birth to a neonate through a vaginal canal that is actively shedding virus will infect the neonate. Because cell-mediated immunity is poorly developed in a neonate, the HSV will not remain local to the infection site. Viremia will lead to disseminated disease. Even with prophylactic treatment, HSV gets into the liver, lung, and brain, resulting in death, intellectual disability, or neurologic disability. **C-section eliminates the risk of neonatal HSV.**

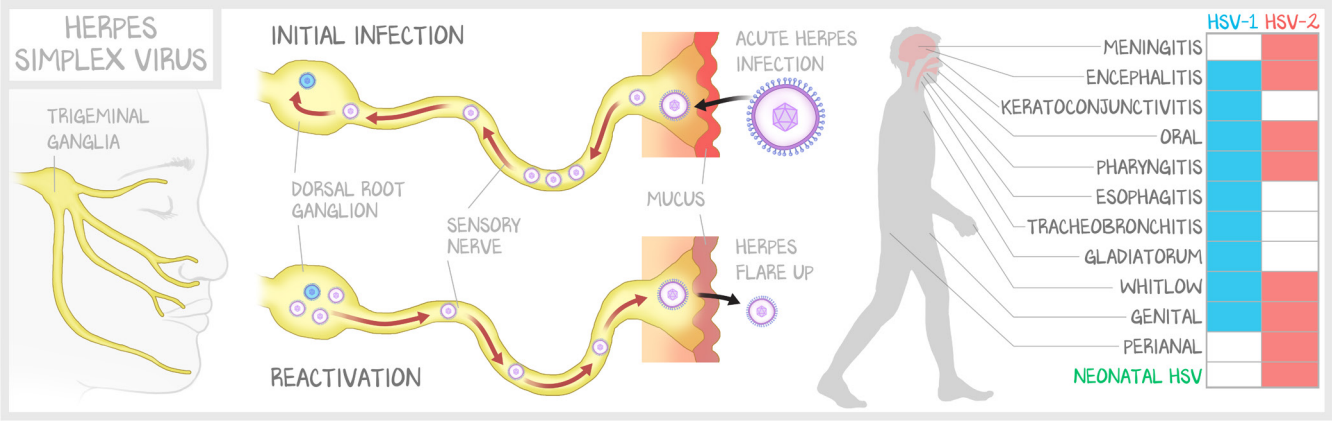

Figure 3.3: Herpes Simplex Virus
The initial infection occurs within the epithelium that had contact with the virus. The sensory nerves whose axons innervate the affected tissue—and only those neurons—get infected, too. Each neuron has a dormant virus within it—a latent infection. If, at any time, one virus in one neuron reactivates, that neuron will die. Before it does, many viruses will travel down the sensory axon and infect the epithelium the sensory nerve innervates. HSV-1 is by far more common than HSV-2. Given its prevalence, it is more likely to cause a nonsexual disease—oral, pharyngeal, esophageal, tracheal. HSV-2 was formerly the HSV of sexually transmitted disease. The overlap has made the distinction between HSV-1 and HSV-2 essentially irrelevant, except that neonatal HSV continues to be predominantly HSV-2.

Everything described above represents the **acute disease**. HSV-1 and HSV-2 are also **latent** viruses. They hide in the neurons of sensory fibers as described at the end of the last section. They do not replicate while latent. There are no symptoms while latent. Once infected with HSV, there is no eradicating it. Acyclovir reduces the duration of acute reactivation and helps encephalitis heal. Latent infections **reactivate at the same region as the acute infection**. Dissemination can occur with profound immunocompromise, but generally do not.

(a) (b) (c)

Figure 3.4: Vesicles on an Erythematous Base
Any one lesion may be described as a vesicle on an erythematous base. HSV-1 and HSV-2 are essentially indistinguishable. (a) An HSV-1 fever blister is an isolated lesion on the mucocutaneous surface of the lip. (b) HSV-2 on genitalia occurs on mucosal surfaces (vagina) and cutaneous surfaces (penis). (c) Varicella-zoster also may appear as a vesicle on an erythematous base. However, in primary disease it is always disseminated; in reactivation, it is dermatomal.

Varicella-Zoster Virus (VZV)

Varicella-zoster is the virus of **chickenpox** (acute infection) and **shingles** (latent infection). It shares many similarities with HSV, which tends to confuse learners. The diseases they cause are superficially similar, but are actually quite different. Like HSV, VZV codes for a thymidine kinase and also its own viral DdDp for replication. Like HSV, its replication of the genome leads to lysis. Like HSV, the symptoms are a vesicle on an erythematous base. Like HSV, it is latent and can reactivate. The similarities end there.

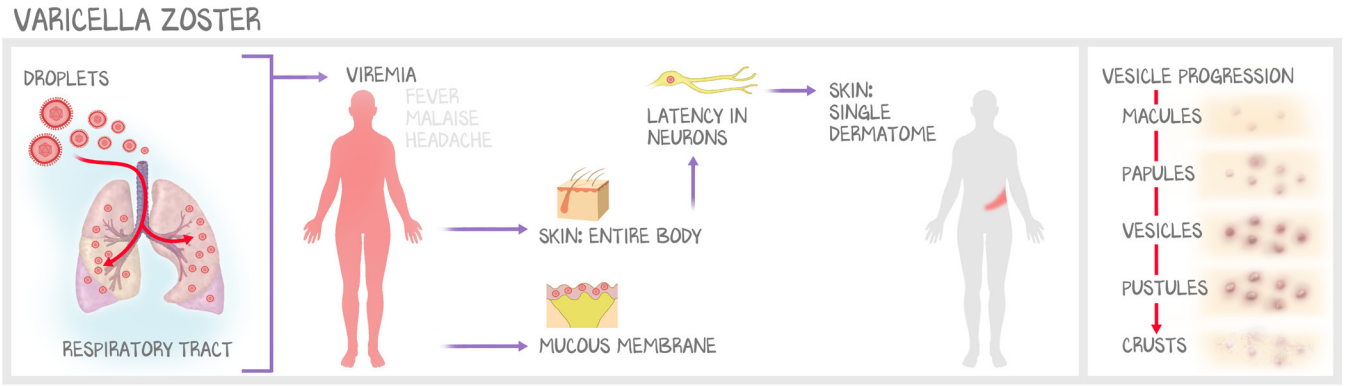

Figure 3.5: Varicella-Zoster Pathogenesis
Varicella-zoster is transmitted by respiratory droplets, inhaled into the lungs, and then spread throughout the body by viremia. Immunization prevents viremia. Viremia brings the virus to mucosa and skin, which generate the disseminated rash—vesicles on an erythematous base. Viremia also distributes the virus to every sensory nerve of every dermatome throughout the body. There it lies dormant. If one virus reactivates in one nerve, the nerve will die. Before it does, the virus will travel down the sensory axon and infect the skin of the dermatome the neuron innervates, leading to shingles.

VZV is **spread through respiratory droplets** that colonize the upper respiratory epithelium. After a two-week incubation period, **viremia** (even in immunocompetent hosts) results in dissemination of the virus everywhere. VZV is one of the five classic childhood exanthems (see parvovirus, above), initially presenting as **fever and a maculopapular rash** distributed over the body. It is truly macular and papular—having both flat areas less than 1 cm and raised lesions less than 1 cm. The lesions are far apart from one another, so they are distinct. Within hours, **thin-walled vesicles on an erythematous base** arise on those spots. Within 12 hours, the vesicles become pustules that eventually crust. Successive crops of lesions occur for 3 to 5 days, so at any one time there may be lesions in multiple stages.

Varicella-zoster then **hides in the dorsal root ganglion** of the associated dermatome, the latent infection. When the host is immunocompromised, it returns, with a **painful burning prodrome** and an eruption of lesions. There is an eruption of vesicles on an erythematous base. The lesions of the reactivation infection are **confined to one dermatome**, and therefore **never crosses midline**. The reactivation lesion is called shingles. It is also called herpes zoster. We will not use the term herpes zoster again—the term confuses learners who believe it to be HSV-related. You may be thinking to yourself, "*vesicles on an erythematous base? Hides in the dorsal root ganglion? Isn't that HSV?*" Only in the sense that they sound like one another in a vignette. Varicella is respiratory droplets, goes viremic, infects every neuron, and happens to reactivate in a dermatome. Herpes Simplex Virus is spread through direct contact, infects only a few neurons of the skin infected, and reactivates at the exact same spot as that neuron.

Like HSV, acyclovir can mitigate duration of symptoms, but cannot cure. But there is a something better than medication for VZV. We have developed both a vaccine for those living with latent infections (the "shingles shot") and a **live attenuated vaccine** that we can use to vaccinate children and at-risk adults ("chickenpox shots"). NO MORE POX PARTIES! Contracting VZV as an adult generally results in a more severe eruption of lesions, and children infected on purpose were considered immune to VZV. So pox parties were where children were sent in to play with actively symptomatic children. This practice prevented bad pox disease, but also ensured that every adult put through that process was at risk for reactivation as shingles. Now, for those children who have not had chickenpox, the childhood vaccine will prevent chickenpox, and therefore they will never be at risk for shingles.

Epstein-Barr Virus (EBV)

EBV causes **infectious mononucleosis** ("mono" or the "kissing disease"). The classic triad is **lymphadenopathy** (swollen lymph nodes), **splenomegaly** (large spleen), and **exudative pharyngitis** (pus in the back of the throat). If you only heard the complaint of the pharyngitis, you might treat this with penicillin, presuming it was a strep throat. If penicillin is given to EBV, there will be a rash. This rash is not a penicillin allergy, but a diagnostic clue that what you are treating is not strep throat. It is spread via **respiratory droplets** and **mucosal contact** (sharing drinks or swapping spit). 80% of people entering college are already seropositive for EBV, but never actually got the symptoms of the disease. For those who have symptoms, EBV gets into the **pharynx**, causing a pharyngitis (pain and pus). The virus gets into **B cells** (the site of latency) and can immortalize them (via transformation). The virus is transported to the lymph nodes and spleen, where it replicates, inducing B-cell proliferation. B-cell proliferation triggers T-cell activation. The fever, fatigue, and malaise that accompany the classic triad are a product of T-cell activation. B cells are infected, B cells are induced to proliferate, and T cells get activated. Where those cells are—the spleen and the lymph nodes—enlarges.

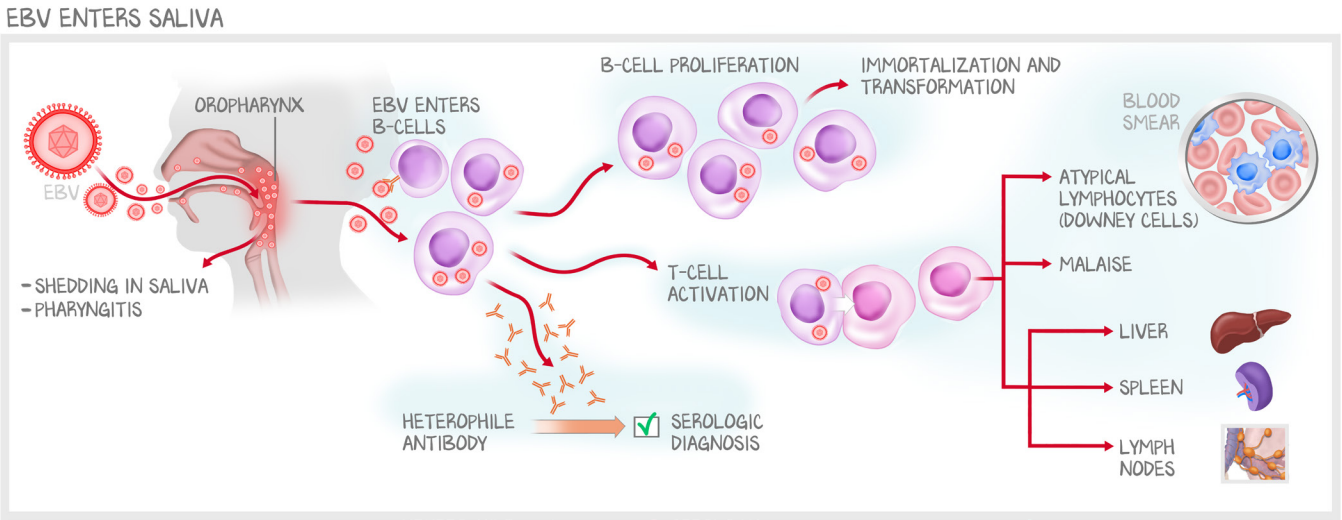

Figure 3.6: Epstein-Barr Pathogenesis
EBV in the saliva infects a new host. Inflammation of the infected mucosa leads to pharyngitis. At the same time, EBV induces B-cell proliferation, leading to the formation of antibodies, which allows serologic diagnosis. B-cell proliferation leads to T-cell activation, which produces symptoms and the blood smear findings. Ongoing T-cell activation results in proliferation of secondary lymph organs, leading to splenomegaly and lymphadenopathy.

If a biopsy of lymph node were taken, there would be the intranuclear inclusion body just like the other herpesviruses. But we don't diagnose EBV that way. It isn't necessary, and getting to a lymph node with a scalpel isn't without risk. So, in addition to the inclusion bodies you would expect in infected cells, EBV gives us an antibody and a blood smear. On **blood smear** you can see **atypical lymphocytes** (also called Downey cells). Because there is B-cell proliferation, an antibody is made, the **heterophile antibody**, which provides a method for serologic diagnosis. There is no treatment or vaccine for EBV. The earlier the patient is exposed, the less severe the disease is. Infection confers lifelong immunity.

Except if you get AIDS. Since EBV can get into the lymph nodes, induce replication, and immortalize B cells within those lymph nodes, it should not be surprising to see that the possible sequelae include lymphoma. If a patient becomes immunocompromised and has a latent infection, a long-term consequence could be either **Hodgkin's lymphoma** or and **Burkitt's lymphoma**.

Cytomegalovirus (CMV)

CMV is everywhere. Almost all patients have CMV antibodies. Most patients do not suffer symptoms. CMV isn't a virus we should concern ourselves with, because everyone is exposed, immune, and asymptomatic. But now that we have transplants (requiring immunosuppression), and AIDS, and because CMV causes birth defects, we still have to keep our eye on it.

CMV should be seen as the "other EBV." While the presentation is usually asymptomatic, some patients may have the syndrome of infectious mononucleosis, but will be **heterophile-Ab negative** and not present with atypical lymphocytes. EBV and CMV both can cause infections of the brain, liver, heart, etc., with profound immunocompromise. But CMV is usually worse AND it CAN be treated. Disseminated CMV is fatal. An active CMV infection needs to be treated. It is diagnosed with **CMV PCR**. A biopsy will show perinuclear halos and inclusion bodies because it is a herpesvirus. Not good enough—the PCR tells us for sure. Because **CMV does not have a thymidine kinase** like the rest of the herpesviruses, we cannot use acyclovir, but instead we must use **ganciclovir**. There is no vaccine, though most humans already have immunoglobulins to it. It's when the immune system catastrophically fails and those antibodies can't do anything, that we have problems.

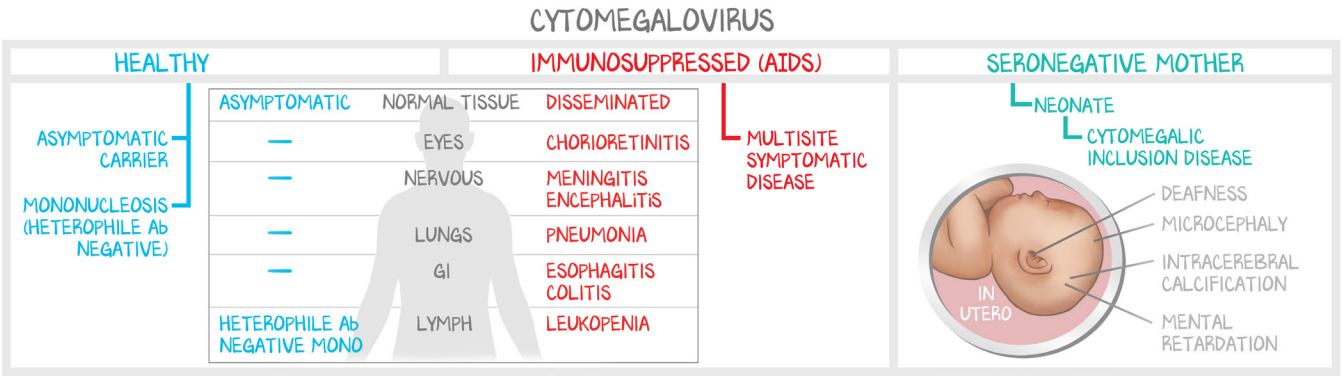

Figure 3.7: Cytomegalovirus Pathogenesis
CMV rarely has any symptomatology in healthy patients. If anything, it will be a self-limiting, heterophile-negative infectious mononucleosis. In profound immunocompromise, CMV can infect all organs, and do so severely. In a pregnant woman who is exposed to CMV for the first time, she will have hardly any symptoms, but her baby will suffer deafness, microcephaly, and intracerebral calcifications that will cause intellectual disability.

CMV **can cross the placenta** and cause **congenital defects**. Congenital CMV causes vision loss, hearing loss, and mental retardation. Microcephaly and intracerebral inclusion bodies are often seen as well. For this to happen, mom must be unexposed to CMV, so not have developed antibodies to CMV, then get pregnant, THEN get exposed to CMV. The primary infection and viremia cause congenital CMV. Any other exposure, and baby has no issues.

Human Herpes Virus 6 and 7

HHV-6 and HHV-7 are herpesviruses that cause the child exanthem disease **roseola** (exanthem subitum). A child will present with a very high fever. When the fever breaks, there is a rash that starts on the trunk and spreads to other parts of the body. There is no vaccine, no treatment, and no long-term sequelae. In Pediatrics, as part of the clinical sciences, we spend more time on this virus. For the basic sciences, it is of limited yield.

Human Herpes Virus 8, aka Kaposi's Sarcoma

A person with AIDS and HHV-8 is at risk for developing Kaposi's sarcoma. Little is known about HHV-8. It is believed to be a sexually transmitted infection. Its genes code for anti-apoptosis homologs, proteins that are similar in structure and function to host cell proteins. Examples include IL-6 and BCL-2 homologs. Like EBV, HHV8 hides in B cells. Like EBV, it is implicated in malignancy. Kaposi's sarcoma is the most common cancer in sub-Saharan Africa. Kaposi's sarcoma is extraordinarily rare in the United States, and will be seen only in severe AIDS.

Patches of abnormal tissue, made of cancerous cells and blood vessels, appear anywhere on the body, under the skin on visceral organs, and in hollow organs. They appear red or purple.

Hepatitis B Virus (Hepadna)

Hepadnaviruses have their own lesson and are discussed in Viruses #7: *Hepatitis Viruses*. Hepatitis B is the only viral hepatitis that is a DNA virus. Thus its name, hepa- (hepatitis) -dna (DNA virus).